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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/529,795	04/20/2000	HARTMUT KUPPER	0480/001178	4157

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EXAMINER	
SEHARASEYON, JEGATHEESAN	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 08/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/529,795	KUPPER ET AL.	
	Examiner	Art Unit	
	Jegatheesan Seharaseyon	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to the amendment and remarks filed on 4/22/04. Applicant has amended claims 1-4 and 7. Claims 1-7 are pending.

2. The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office action.

3. Any objection or rejection of record, which is not expressly repeated in this action, has been overcome by Applicant's response and withdrawn.

Claim Rejections - 35 USC § 112, withdrawn

4. Applicant's amendment of claim 1 necessitates the withdrawal of rejection under 35 U.S.C. 112, second paragraph for omitting essential steps. Further, Applicant's arguments with respect to the definition of septic disorders is persuasive, thus necessitating the withdrawal of rejection under 35 U.S.C. 112, second paragraph.

Claim Rejections - 35 USC § 101, withdrawn

5. Upon further consideration and pursuant to Applicant's arguments which persuasive the rejection of claim 7 under 35 U.S.C. 101 is withdrawn.

Claim Rejections - 35 USC § 102

6. Applicant's amendment of claim 1 and 2 necessitates the withdrawal of rejection under 35 U.S.C. 102(e). However, Applicant's amendment of claim 4 does not obviate the rejection, as being anticipated by Stenzel et al. for reasons of record set forth in the Office Action of 12/17/2003 page 4. Stenzel et al. describe the use of $F(ab')_2$ fragment of a monoclonal anti-TNF antibody as TNF antagonist (see column 3 and 4). Therefore, claim 4 remains rejected under 35 U.S.C. 102(e) as being anticipated by Stenzel et al.

Claim Rejections - 35 USC § 103

7. Claims 1 (amended), 2 (amended), 3 and 5-7 remain rejected under 35 USC § 103 as being obvious over Stenzel et al. (U.S. Patent NO: 6, 235, 281 or WO95/20978) in view of Kragsbjerg et al. (1996) for reasons set forth in Paper No: 12 and Office Action of 12/17/2003. Applicant's arguments filed on 4/22/04 have been fully considered but are not persuasive. The Applicant alleges that the Office reasons that an increase in the IL-6 level is inherent in any septicemia patients having IL-6 levels of 500pg/ml and more, as IL-6 is not detectable in healthy individuals. The Office merely cited Applicant's own work in the '281 patent, which recited that the "normal" IL-6 serum levels are usually below detection limits to a maximum of 20pg/ml. Further, '281 patent teaches that septicemic patients with IL-6 levels of 500 pg/ml or more including levels above 1000 pg/ml respond well to the treatment with TNF antagonists (see column 2, lines 15-20). Contrary to Applicant's assertion that that the Office requires that measurements be taken while the patients is healthy and asymptomatic, the measurements are taken of patients with septicemia or sepsis. Furthermore, the term patient by definition implies that the individual is "unhealthy". In addition, Stenzel recognizes that in patients with septicemia the IL-6 levels are higher compared to the normal serum levels.

Applicant also alleges that the citation cannot fairly be interpreted to suggest that treatment will be more successful in more severe cases that less severe ones. However, Stenzel et al. addressed this. The '281 patent states that, in the patients with IL-6>1000 pg/ml there was a dose-dependent reduction in the mortality on treatment with anti-TNF antibody fragment from 80.0% (=placebo group) to 36.4% (1.0 mg/kg

antibody). In the patients with IL-6<1000 pg/ml, the mortality was not reduced by treatment with anti-TNF antibody fragment, on the contrary it was slightly increased (30.4% in the placebo group compared with 38.9% in the group with 1.0 mg/kg antibody). The result of this clinical study clearly proves that treatment of severe septicemia with anti-TNF antibodies is successful only when the treated septicemic patients have a serum level of IL-6>1000 pg/ml; treatment of patients with serum levels of IL-6<1000 pg/ml is unsuccessful and sometimes even contraindicated. Contrary to Applicant's assertion that the reference does not mention measuring for an increase over time in an individual patient, Kragsbjerg et al. determines the blood cytokine levels in 27 patient samples at admission, after 1, 4, 12, 18 and 24 hrs (see abstract). There is recognition that IL-6 increases in septicemic patients compared to healthy individuals (column 2, lines22-27; Stenzel et al.). It also should be noted that, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Therefore claims 1-3 and 5-7 remain rejected under 35 USC § 103 as being obvious over Stenzel et al. (U.S. Patent NO: 6, 235, 281 or WO95/20978) in view of Kragsbjerg et al. (1996).

Double Patenting

8. The rejection of claims 1-7 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. U.S. Patent No: 6,235,281 in view of Kragsbjerg et al. (1996) is maintained. Applicant's arguments

filed on 4/22/04 have been fully considered but are not persuasive for reasons set forth in Paper No: 12, the Office Action of 12/17/2003 and above in paragraph 8.

9. No claims are allowable.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 571-272-0892. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone

number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JS 07/04

Brenda Brumback

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